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REMARKS

Applicants submit herein remarks to the issues set forth in the Final Office Action dated June 22, 2001, to the extent that the issues apply to the newly added claims.

Claims 1, 4-10, 16-19, 24-27, 31, 34-63, 65, and 104-129 were pending the application. Claims 1, 4-10, 16-19, 24-27, 31, 34-63, 65, and 104-129 have been canceled, without prejudice, and new claims 130-162 have been added. Upon entry of this amendment, claims 130-162 will be pending. For the Examiner's convenience the currently pending claims are set forth in Appendix A.

Support for new claims 130-162 may be found throughout the specification, including the originally filed claims. Specifically, support for claim 130 can be found at least at page 2, lines 13-15 and lines 24-33 of the specification; support for claim 131 can be found at page 3, lines 34-38 of the specification; support for claim 132 can be found at page 3, lines 25-28 of the specification; support for claim 133 can be found at page 3, line 37 through page 4, line 3 of the specification; support for claims 134-137 can be found at page 3, lines 1-10 of the specification; support for claims 138-148 can be found at page 6, lines 33-37 of the specification; support for claim 149 can be found at page 17, lines 14-15, and at page 27, lines 8-10 of the specification; support for claims 150-151 can be found at page 3, lines 15-18 of the specification; support for claim 152-153 can be found at page 3, lines 25-29 of the specification; support for claims 154-157 can be found at page 3, line 31 through page 4, line 4 of the specification; support for claim 158 can be found at page 14, lines 15-34 of the specification; support for claims 159-162 can be found at page 4 lines 5-14 of the specification.

Applicants submit herewith a copy of the abstract on a separate page.

No new matter has been added. Any amendments to and/or cancellation of the claims was done solely for the purpose of expediting prosecution of the present

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application. Applicant reserves the right to pursue the subject matter of the claims as originally filed in this or a separate application(s).

Acknowledgement of Telephonic Interview with the Examiner

Applicants gratefully acknowledge the telephonic interview with the Examiner in the parent application. The claims being submitted in the enclosed Preliminary Amendment were discussed during this telephonic interview.

Rejection of Claims Under Nonstatutory Double Patenting

Claims 1, 4-10, 16-19, 24-27, 31, 34, 47, 48, 50-55, 65, and 122-129 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-9 of U.S. Patent No. 6,037,138. In view of the cancellation of claims 1, 4-10, 16-19, 24-27, 31, 34, 47, 48, 50-55, 65, and 122-129, the rejection is obviated. However, to the extent that the rejection may apply to any of the claims presented herein, Applicants will consider the rejection upon a finding that the application is otherwise in condition for allowance.

Objection that Claims Presented Are Not Properly Searchable

Applicants believe that the claims as file herein are properly searchable.

Rejection of Claims Under 35 U.S.C. §112, First Paragraph

Claims 1, 4-10, 16-19, 24-27, 34, 47, 48, 50-55, 65, 122, 124, 126, and 128 are rejected under 35 U.S.C. §112, first paragraph because

the specification...does not reasonably provide enablement for a 'matrix metalloproteinase or cancer.' The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the claimed invention commensurate in scope with these claims.

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Applicants respectfully traverse the foregoing rejections for at least the following reasons. In view of the cancellation of claims 1, 4-10, 16-19, 24-27, 34, 47, 48, 50-55, 65, 122, 124, 126, and 128 the rejection is obviated. However, to the extent that the rejection applies to new claims presented herein, Applicants provide the following comments of record.

The Examiner further notes that

[c]laims 124, 126, 128 are directed to various cancers such as bladder, renal and lymphomas in general, and other claims include other tissues, but no such types of cancer of such tissues are enabled by the present specification.

The Examiner acknowledges that "while possibly being enabling for specific enzymes and prostate cancer, [the specification] does not reasonably provide enablement for 'a matrix metalloproteinase or cancer.'" Applicants submit that the instant specification **fully enables** specific enzymes, prostate cancer, matrix metalloproteinases, and cancer. Moreover, the present specification is replete with examples and descriptions of types of cancer that are encompassed by the present invention. It is respectfully submitted that the newly submitted claims are drawn to MMP-associated cancers and are fully enabled. Applicants refer the Examiner to at least following sections of the specification, wherein specific types of cancer are discussed.

- "In a preferred embodiment of the kit, the tissue remodelling-associated conditions being detected are one or more types of cancer, for example, organ-confined prostatic cancer, metastatic cancer, and prognosis of metastasis in a prostate cancer patient." (see page 4, lines 17-20 of the specification).
- "The present invention provides non-invasive methods, between presence of enzymes in biological fluids, and diagnosis and prognosis of tissue remodelling-associated conditions (TRACs), especially cancers, obstructive and degenerative conditions, and arthritic conditions, and kits for use for such diagnosis and prognosis." (see page 4, lines 25-28 of the specification).

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- "The term 'subject,' as used herein, refers to a living animal or human in need of diagnosis or prognosis for, or susceptible to, a condition, in particular an 'tissue remodelling-associated condition' as defined below. The subject is an organism capable of responding to tissue remodelling signals such as growth factors, under some circumstances, the subject is susceptible to cancer and to arthritis." (see page 4, line 34 through page 5, line 3 of the specification).
- "Cancer or neoplasia is characterized by deregulated cell growth and division. A tumor arising in a tissue originating from endoderm or exoderm is called a carcinoma, and one arising in tissue originating from mesoderm is known as a sarcoma (Darnell, J. (1990), *Molecular Cell Biology, Third Ed.*, W.H. Freeman, NY). A current model of the mechanism for the origin of a tumor is by mutation in a gene known as an oncogene, or by inactivation of a second tumor-suppressing genes (Weinberg, R.A., (Sept. 1988), *Scientific Amer.*, 44-51). The oncogenes identified thus far have arisen only in somatic cells, and thus have been incapable of transmitting their effects to the germ line of the host animal. In contrast, mutations in tumor-suppressing genes can be identified in germ line cells, and are thus transmissible to an animal's progeny. **Examples of cancers include cancers of the nervous system, breast, retina, lung, skin, kidney, liver, pancreas, genito-urinary tract, gastrointestinal tract, cancers of bone, and cancers of hematopoietic origin such as leukemias and lymphomas.** In one embodiment of the present invention, the cancer is not a cancer of the bladder. (see page 6, lines 24-37 of the specification). (*Emphasis added*).
- "Metastatic cancer (MC) as exemplified for the purposes of this invention, is not limited to spread of CaP to bone or any particular organ, and includes also spread of other cancers such as kidneys (renal), breast, and gastrointestinal tract to organs beyond these primary sites." (see page 7, lines 36-38 of the specification).

Applicants further teach,

[i]n a preferred embodiment, the enzymes that are detected are matrix-digesting enzymes, more preferably, enzymes that are proteinases, and most preferably, enzymes that are metalloproteinases. **In a different aspect, the methods of this invention involve enzymes that are full-length active enzymes, and they are matrix metalloproteinases.** (see page 3, lines 12-15 of the specification).

Thus, Applicants respectfully request that the Examiner withdraw this objection under 35 U.S.C. §112, first paragraph.

The Examiner is also of the opinion that

regarding the claims directed to a gelatinase, it appears in the Tables in the present specification that not all gelatinases are effective in the claimed

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invention, only possibly two may be and they are not characterized in any meaningful way.

Applicants respectfully traverse the foregoing rejection and submit that Applicants' specification fully enables 'a gelatinase.' Specifically, Applicants teach examples of MMPs, which are the type IV collagenases, *e.g.*, mmp-2 (gelatinase A, EC 3.4.24.24) and mmp-9 (gelatinase B, 3.4.24.35), and stromelysins (EC 3.4.24.17 and 3.4.24.22) (see page 11, lines 8-10 of the specification). Furthermore, Applicants set forth ten working examples wherein, "specimens were analyzed by gelatin zymography, and the results were recorded as positive for each protein band with gelatinase activity observed in the lane corresponding to that urine sample" (see page 18, lines 34-36 of the specification). Examples 1-10 confirm the teachings of the instant invention; namely, the value of urine MMP zymogram routine analysis in order to detect the presence of cancer in particular, as an example of a tissue remodelling-associated condition, and for monitoring of cancer patients during therapy, and for prognosis of the course of cancer and the appearance of metastases. Therefore, Applicants respectfully request that the Examiner withdraw this rejection.

The Examiner is also of the opinion that "'a matrix metalloproteinase' reads on a multitude of Calpains among many other enzymes which are unlikely to work in the claimed invention." Applicants respectfully traverse the foregoing rejection for at least the following reasons. There are four classes of hydolytic enzymes based on the catalytic group at their active center: serine/threonine, cysteine, aspartic and metallo (see Shapiro, S., Matrix metalloproteinase degradation of extracellular matrix: biological consequences (1998) *Cell Biology* 10:602-608, provided herewith as Appendix B). Table 1 of Appendix B sets forth known MMP members and illustrates that there are many metalloproteases that are not *matrix* metalloproteinases. The Calpains, for example, "form a growing family of structurally related intracellular multidomain *cysteine*

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proteinases containing a papain-related catalytic domain, whose activity depends on calcium." (see Reverter, D. *et al.*, The structure of Calcium-Free Human m-Calpain. Implications for calcium Activation and Function. (2001) *Trends Cardiovascular Medicine* 11(6):222-9, provided herewith as Appendix C). A matrix metalloprotease does not read on a multitude of Calpains, as asserted by the Examiner, because the matrix metalloprotease family does not encompass Calpains. In summary, a Calpain is not a metalloprotease, and therefore, not a matrix metalloprotease. Applicants therefore respectfully request that the Examiner reconsider and withdraw this rejection.

The key question then, is whether it would require undue experimentation to use the claimed methods. Enablement is not precluded by the necessity for some experimentation, and a considerable amount of experimentation is permitted. See, *In re Wands*, 8 U.S.P.Q. 2d 1400, 1404 (Fed. Cir. 1988). Based on the teachings of the specification as enumerated and cited above and the state of the art at the time the application was filed, Applicants submit that one skilled in the art would be able use the claimed methods without undue experimentation.

In view of the foregoing, Applicants respectfully submit that the present invention satisfies the requirements of 35 U.S.C., 112, first paragraph.

Rejection of Claims Under 35 U.S.C. §112, Second Paragraph

The Examiner has rejected claims 112-129 under U.S.C. §112, Second Paragraph, as being "indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." It is respectfully submitted that the above rejection does not pertain to the newly submitted claims.

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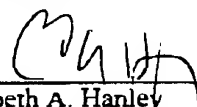
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CONCLUSION

In view of the foregoing amendments and foregoing remarks, it is respectfully submitted that the application is in condition for allowance. If a telephone conversation with Applicants' Attorney would expedite the prosecution of the above-identified application, the Examiner is urged to call Applicants' Attorney at (617) 227-7400.

Respectfully submitted

LAHIVE & COCKFIELD, LLP


Elizabeth A. Hanley
Registration No. 33,505
Attorney for Applicants

28 State Street
Boston, MA 02109
Telephone: (617) 227-7400
Facsimile: (617) 742-4214

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